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Prostate Cancer

Development and Internal Validation of a Web-based Tool to Predict Sexual, Urinary, and Bowel Function Longitudinally After Radiation Therapy, Surgery, or Observation

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Abstract

Background: Shared decision making to guide treatment of localized prostate cancer requires delivery of the anticipated quality of life (QOL) outcomes of contemporary treatment options (including radical prostatectomy [RP], intensity-modulated radiation therapy [RT], and active surveillance [AS]). Predicting these QOL outcomes based on personalized features is necessary.
Objective: To create an easy-to-use tool to predict personalized sexual, urinary, bowel, and hormonal function outcomes after RP, RT, and AS.
Design, setting, and participants: A prospective, population-based cohort study was conducted utilizing US cancer registries of 2563 men diagnosed with localized prostate cancer in 2011–2012.
Intervention: Patient-reported urinary, sexual, and bowel function up to 5 yr after treatment.
Outcome measurements and statistical analysis: Patient-reported urinary, sexual, bowel, and hormonal function through 5 yr after treatment were collected using the 26-item Expanded Prostate Index Composite (EPIC-26) questionnaire. Comprehensive models to predict domain scores were fit, which included age, race, D'Amico classification, body mass index, EPIC-26 baseline function, treatment, and standardized scores measuring comorbidity, general QOL, and psychosocial health. We reduced these models by removing the instrument scores and replacing D'Amico classification with prostate-specific antigen (PSA) and Gleason score. For the final model, we performed bootstrap internal validation to assess model calibration from which an easy-to-use web-based tool was developed.

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Results and limitations: The prediction models achieved bias-corrected R-squared values of 0.386, 0.232, 0.183, 0.214, and 0.309 for sexual function, urinary incontinence, urinary irritative, bowel, and hormonal domains, respectively. Differences in R-squared values between the comprehensive and parsimonious models were small in magnitude. Calibration was excellent. The web-based tool is available at https://statez.shinyapps.io/PCDSPred/.

Conclusions: Functional outcomes after treatment for localized prostate cancer can be predicted at the time of diagnosis based on age, race, PSA, biopsy grade, baseline function, and a general question regarding overall health. Providers and patients can use this prediction tool to inform shared decision making.

Patient summary: In this report, we studied patient-reported sexual, urinary, hormonal, and bowel function through 5 yr after treatment with radical prostatectomy, radiation therapy, or active surveillance for localized prostate cancer. We developed a web-based predictive tool that can be used to predict one's outcomes after treatment based on age, race, prostate-specific antigen, biopsy grade, pretreatment baseline function, and a general question regarding overall health. We hope both patients and providers can use this tool to better understand expected outcomes after treatment, further enhancing shared decision making between providers and patients.

1. Introduction

As more data accumulate highlighting the favorable long-term survival of men with localized prostate cancer regardless of treatment modality, a better understanding of the associated risks of treatment is of paramount importance [1,2]. Nevertheless, the optimal treatment is patient specific and depends on a myriad of factors, including overall health; risk of cancer progression; baseline urinary, sexual, and hormonal function; and patient preference. While a comparison of the effectiveness and harms of radical prostatectomy (RP), external beam radiation therapy (EBRT), and active surveillance (AS) has previously been reported in a generalized fashion [3], devising a method to disseminate this information in a way that is patient specific, easy to access, and similarly easy to comprehend remains elusive.

Over the past decade, patients have become increasingly aware of predictive tools to actively participate in their own decision making [4]. Providers have also desired such tools in order to explain possible treatment outcomes and side effects. Quality of life (QOL) outcomes after surgery or radiotherapy depend on the severity of the cancer at diagnosis [5]; baseline urinary, sexual, and bowel function; age; and comorbidity [6]. Nevertheless, a model predicting functional outcomes of contemporary treatments after accounting for patient-specific factors does not exist yet. In this context, we analyzed patient-reported functional outcomes from the Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) study, a multicenter, prospective, population-based study of men diagnosed with localized prostate cancer that contains baseline information and longitudinal outcomes through 5 yr [7]. We then developed and validated an easy-to-use web-based tool to predict personalized sexual, urinary, bowel, and hormonal function after RP, RT, and AS, which can easily be accessed by both patients and providers alike.

2. Patients and methods

2.1. Study population

The CEASAR study is a multicenter, longitudinal, population-based, and prospective observational cohort study of men diagnosed with localized prostate cancer from 2011 to 2012, designed to quantify the effectiveness and harms of contemporary treatment strategies, focusing on functional outcomes (NCT0136286). The methodology has been described previously [7]. A total of 3709 men were enrolled from 2011 to 2012. Eligibility criteria included men $\leq$80 yr of age with clinical cT1 or cT2 disease, a prostate-specific antigen (PSA) level of $<$50 ng/dl, no nodal involvement or metastases on clinical evaluation, and being enrolled within 6 mo of diagnosis.

Patient-reported outcomes were collected via mail survey at enrollment, and at 6, 12, 36, and 60 mo after enrollment. A medical chart review that included both clinical and treatment information was obtained at 12 mo, and Surveillance, Epidemiology, and End Results (SEER) registry data were linked to the data set. This study includes follow-up through September 2018. Vanderbilt and each corresponding SEER sites obtained approval from their local institutional review boards.

2.2. Data outcomes

The primary outcome was a patient-reported disease-specific function, defined as a domain score on the validated 26-item Expanded Prostate Index Composite (EPIC-26) questionnaire [8]. EPIC evaluates function and bother for sexual, urinary, bowel, and hormone domains as continuous measures on a scale of 0–100, with higher scores indicative of better function. Previously published and validated domain score thresholds (clinically relevant point changes: bowel, 4–6; hormone, 4–6; urinary irritative, 5–7; urinary incontinence, 6–9; sexual, 10–12) were used to assist in

determining minimal clinically important changes in domain scores [9].

Patient surveys included questions on patient-reported age at diagnosis, income, race, educational attainment, employment or retirement status, marital status, insurance coverage, general health and function (Medical Outcomes Study Short Form 36 [SF-36]), physical function, emotional health, social support, cancer-related anxiety, psychosocial health, general QOL, energy and fatigue, and a depression scale (the Center for Epidemiologic Studies Depression scale) [10–12]. Enrolled patients also completed the Total Illness Burden Index for prostate cancer, a validated patient-reported 84-item comorbidity assessment of 11 health domains modified for patients with prostate cancer [13,14]. Finally, PSA levels, body mass index (BMI), treatment type, and tumor characteristics, including biopsy grade and stage, were obtained by abstracting data from medical records. Patients who received primary androgen-deprivation therapy, brachytherapy, or cryoablation were excluded.

2.3. Statistical analysis

Descriptive statistics on demographic and baseline clinical variables were presented as the median with quartiles for continuous variables and the frequency with percentages for categorical variables. To model the EPIC domain scores over time, we fit longitudinal regression models as a function of treatment, time since treatment, and their interaction. To account for the correlation due to repeated measurements, we used generalized estimating equations with an independent weight matrix. Robust variance-covariance matrices were estimated using the Huber-White method (Supplementary material) [15,16]. For each functional domain, we first fit the comprehensive models that were developed in our previous work (denoted as the "full model" hereafter), in which treatment choice, time since treatment, age, race, comorbidity, prostate cancer risk stratum, physical function, social support, depression, medical decision-making style, study site, and baseline EPIC domain score were included as predictors.

With the goal of developing a parsimonious, flexible, and readily applicable clinical model, we made an a priori decision to exclude comorbidity, social support, depression, and medical decision-making style, which are burdensome for the patient to report and/or may not be known to the patient. Additionally, the study site is not included in these reduced models.

We replaced the D'Amico prostate cancer risk stratum (defined by clinical stage, tumor grade on biopsy, and PSA) [17] with PSA and grade on biopsy because we anticipated that the other component, clinical stage, is not always readily known by the patient. Without increasing the data-entry burden to the patient, we further included the interaction terms between time since treatment and the three most important predictors: age, treatment choice, and baseline domain score. This resulted in a parsimonious and enriched final model (denoted as the "final model" hereafter) that included treatment choice, age, race, PSA, Gleason score, a question on overall health, baseline EPIC domain score, and the aforementioned interaction terms.

In all models, restricted cubic splines were used for continuous or nominal variables with five knots to relax the assumption of linear association between predictors and outcomes. Multiple imputation was used for missing covariates, as we have previously done [3,18,19]. Briefly, the Multiple Imputation using Chained Equation (MICE) procedure was used: modeling each covariate as an outcome in a regression model and all other covariates as predictors. This procedure generated multiple ($n = 30$) complete datasets. Next, the prediction model was fit on each of these datasets. The final model coefficients were the average of the coefficients from these 30 models, and the final model variances of the coefficients were calculated from both within and between model variances. The proportion of data missing prior to multiple imputations for all models is found in Table 1.

While severe overfitting is unlikely given the sample size, we performed 300-iteration bootstrap internal validation to assess the degree of optimism for each model. Bias-corrected R-squared values were reported as the measurements of model performance. In addition, model calibration was assessed graphically with bootstrap-based calibration plots [20]. Statistical significance was assessed at a two-sided 5% level. All statistical analyses were performed using R software version 3.4 [21]. Finally, we developed a web-based interactive tool based on the final models. We developed this prediction tool in compliance with the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) checklist (Supplementary Table 1) [22].

3. Results

3.1. Baseline patient characteristics and demographics

Altogether, the parent study accumulated 3709 men, of whom 432 were excluded for failing to meet the basic inclusion criteria. A total of 521 additional men were excluded for receiving treatment other than AS, EBRT, or RP, leaving 2756 men for consideration (Supplementary Fig. 1). A total of 2563 men completed a baseline survey and at least one survey thereafter (94.9%). Survey response rates were 89% at 6 mo, 86% at 12 mo, 78% at 36 mo, and 70% at 60 mo, and 1755 patients (68.4%) completed all surveys at every time point. Descriptive characteristics for the overall cohort are reported in Table 1. Altogether, the population was diverse with respect to age, race, and disease severity. Of the men in the AS cohort, 26.0% eventually underwent RP or EBRT, but were categorized as AS.

The web-based tool may be found at https://statez.shinyapps.io/PCDSPred/.

3.2. Sexual domain

The full and final models performed similarly, with an adjusted R-squared value in the full model of 0.391 versus a bias-corrected R-squared value in the final model of 0.386,

Table 1 – Demographics and baseline characteristics.

Demographics	N	Participants (N = 2563)
Age (yr), median (IQR)	2563	64 (58, 69)
Race	2547	
White		74% (1884)
Black		14% (359)
Hispanic		7% (187)
Asian		3% (80)
Other		1% (37)
Education	2433	
<High school		10% (250)
High school graduate		21% (500)
Some college		22% (533)
College graduate		23% (562)
Graduate or professional school		24% (588)
Marital status	2427	
Married		80% (1953)
Comorbidity score	2445	
0–2		28% (690)
3–4		42% (1024)
≥5		30% (731)
D'Amico prostate cancer risk	2557	
Low risk		45% (1151)
Intermediate risk		39% (988)
High risk		16% (418)
Prostate-specific antigen (ng/ml)	2563	
0–<4		21% (529)
4–<10		66% (1693)
10–<20		10% (257)
20–<50		3% (84)
Clinical stage	2552	
T1		76% (1943)
T2		24% (609)
Biopsy Gleason score	2555	
≤6		52% (1331)
3 + 4		28% (707)
4 + 3		10% (264)
8–10		10% (253)
Any hormone therapy in the 1 st year	2503	
Yes		14% (346)
Accrual site, no. of patients	2563	
Louisiana		28% (725)
Utah		8% (206)
Atlanta		12% (309)
Los Angeles County, CA		29% (731)
New Jersey		16% (411)
Cancer of the Prostate Strategic Urologic Research Endeavor		7% (181)

IQR = interquartile range.

indicating that our model explains 38.6% of the total variation of the domain scores (Table 2). As stated, the final model eliminated BMI and clinical stage, and replaced the D'Amico criteria with the individual items of PSA and Gleason grade. Furthermore, it replaced the SF-36 and standardized instruments measuring comorbidity, depression, social support, physical function, medical decision-making style, and psychosocial health with a single question asking whether the patient's overall health was regarded as "excellent, very good, good, fair, poor, or very poor." This difference in R-squared values between the full and final models (0.391 and 0.386, respectively) was small in magnitude (Table 2). Calibration was excellent (Fig. 1A). The final model included age at diagnosis, race, most recent PSA, Gleason grade, question on overall health, and baseline sexual domain scores of the EPIC-26. Fig. 2 depicts a sample patient with his baseline information and predicted sexual function domain score contingent on treatment type through 5 yr of follow-up.

3.3. *Urinary incontinence, urinary irritative, hormone, and bowel domains*

Analogous to the sexual function domain, the full versus final models performed similarly for the urinary incontinence (adjusted R-squared 0.248 vs bias-corrected R-squared 0.232) urinary irritative (adjusted R-squared 0.220 vs bias-corrected R-squared 0.1843), hormonal (adjusted R-squared 0.350 vs bias-corrected R-squared 0.309), and bowel domains (adjusted R-squared 0.237 vs bias-corrected R-squared 0.214). Differences in R-squared values between the full and final models were small in magnitude. Calibration was also excellent (Fig. 1B–E). An example of a sample patient's predicted urinary incontinence domain score as stratified by treatment type through 5 yr of follow-up is demonstrated in Fig. 3.

4. Discussion

In this multicenter, prospective, longitudinal, population-based, observational cohort study, functional outcomes after treatment for localized prostate cancer can be

Table 2 – Performance of the full and final models for each of the five functional domains.

Functional domain	Original full model	Final enriched model				
	$R^2_{Full\text{-}model}$	RMSE	MAE	R^2_{Raw}	$R^2_{Bias\text{-}corrected}$	Calibration slope
Sexual	0.391	26	21	0.394	0.386	0.990
Urinary incontinence	0.248	23	18	0.242	0.232	0.980
Urinary irritation	0.220	13	9	0.196	0.183	0.970
Bowel function	0.237	11	7	0.227	0.214	0.975
Hormone	0.350	12	9	0.320	0.309	0.982

MAE = mean absolute error; RMSE = rooted mean squared error.
Bias-corrected R^2 values were calculated from 300-iteration bootstraps. Calibration slopes were estimated by regressing the observed domain scores on the predicted domain scores.

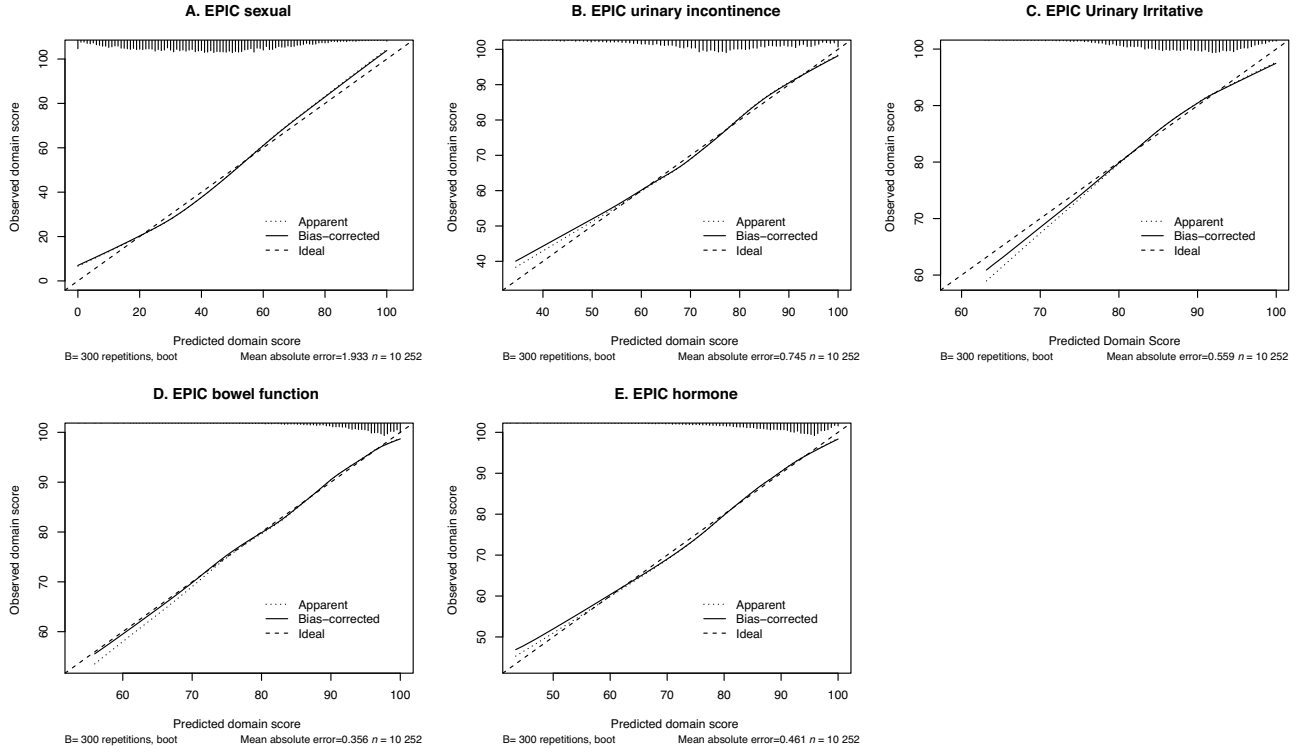

Fig. 1 – Plots of 300-iteration bootstrap calibration for each of the following five EPIC-26 domains: (A) sexual function; (B) urinary incontinence; (C) urinary irritative; (D) hormonal; and (E) bowel function. EPIC-26 = 26-item Expanded Prostate Index Composite.

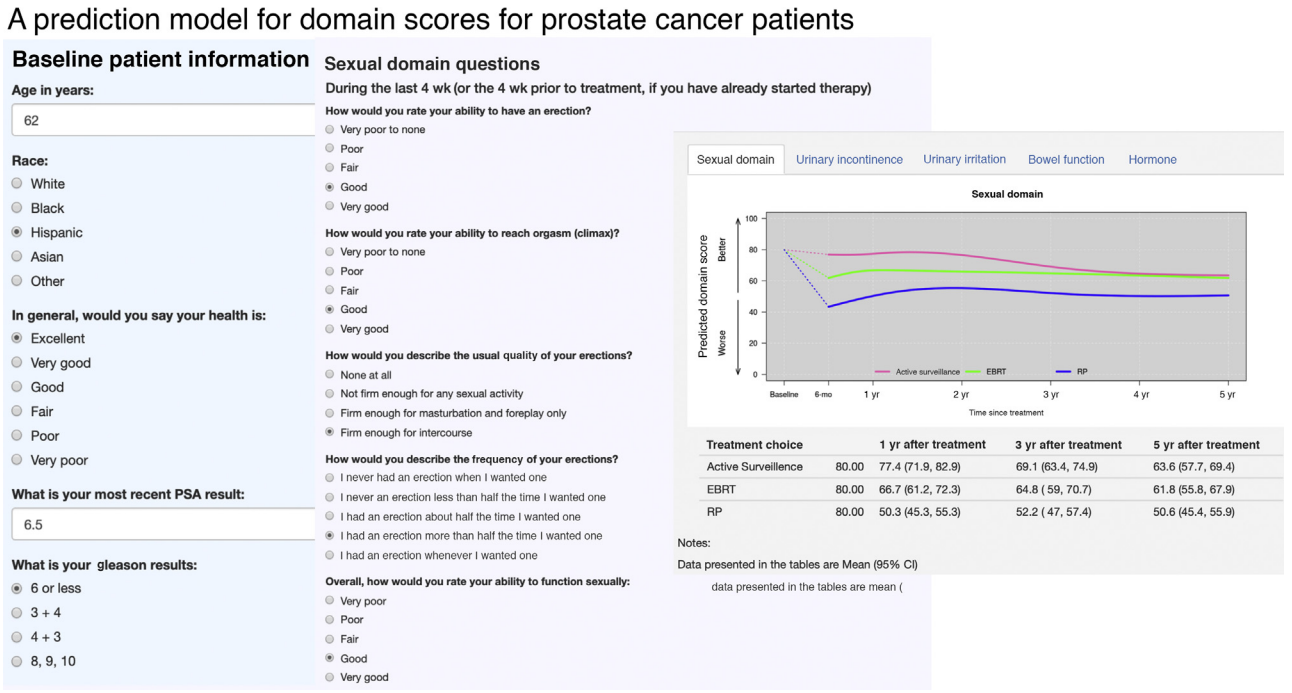

Fig. 2 – An example of a sample patient with their baseline info recorded in the personalized web-based tool and their predicted sexual function domain score depending on treatment through 5 yr of follow-up. The values in parentheses are the 95% confidence intervals. CI = confidence interval; EBRT = external beam radiation therapy; PSA = prostate-specific antigen; RP = radical prostatectomy.

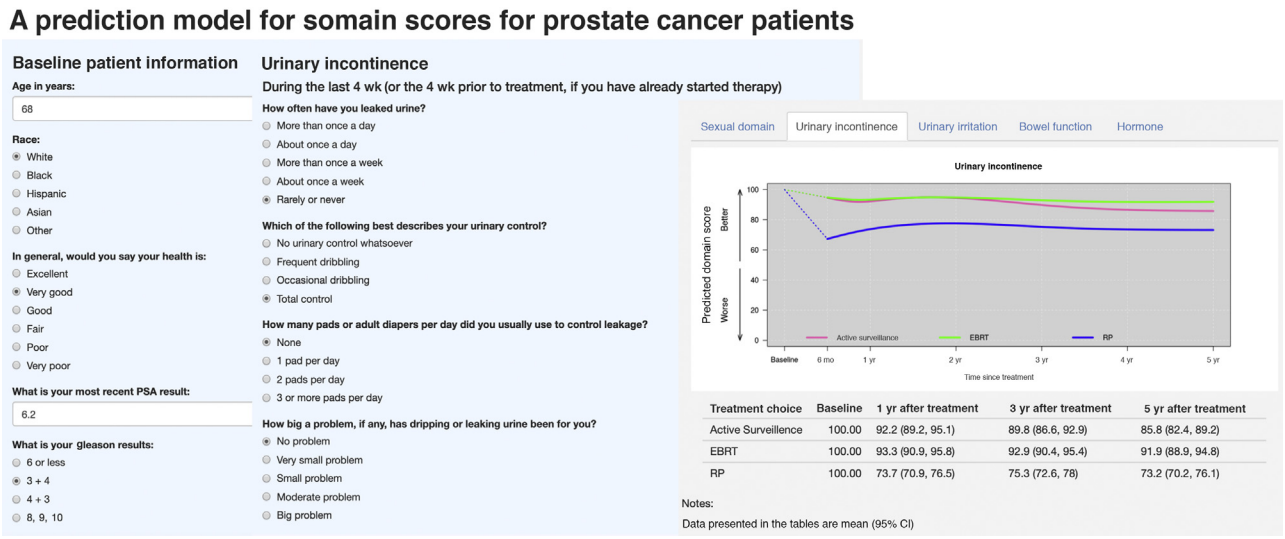

Fig. 3 – An example of a sample patient with his baseline info recorded in the personalized web-based tool and his predicted urinary incontinence domain score depending on treatment through 5 yr of follow-up. The values in parentheses are the 95% confidence intervals. CI = confidence interval; EBRT = external beam radiation therapy; PSA = prostate-specific antigen; RP = radical prostatectomy.

predicted at the time of diagnosis based on age, race, PSA, biopsy grade, baseline function, and a general question regarding overall health. While disseminating accurate information to the patient prior to proceeding with a treatment option is important, being able to individualize a person's expected outcomes is slowly becoming the expectation, adding to the armamentarium of proper counseling. This personalized web-based tool, while containing enough patient-specific information, is not overburdening on the provider, allowing easy implementation. Furthermore, the questions are easy enough for patients to be able to navigate the tool themselves.

With similar adjusted R-squared values between the comprehensive and parsimonious models for each of the five domains, the baseline patient information included was able to remain the same for each domain function outcome. Importantly, there was no notable difference when substituting biopsy grade and PSA for D'Amico risk criteria, which has two benefits. First, a patient is more likely to know his biopsy grade and PSA than the risk stratum he falls into. Second, stage that is based on the digital rectal examination is subjective, and the patient may not be aware of his stage or how that translates into D'Amico risk group. Nevertheless, we found that inclusion of the most recent PSA and biopsy grade is still important. Indeed, previous work by Tyson et al [5] demonstrated that patterns of sexual dysfunction differed according to severity of disease at diagnosis, with low- and intermediate-risk patients having better sexual function scores at 3 yr with EBRT versus RP. Using our personalized tool, this trend is shown to continue through 5 yr.

Previous studies have reported on functional outcome variation due to age [6], race/ethnicity [23], baseline function [3], and cancer severity. Despite these known associations to functional outcome over time, a tool to personalize the effects of these patient-level factors and predict outcomes over time has been lacking. Furthermore, while nomograms and patient-specific predictive tools for survival exist and range from exploring the risk of developing prostate cancer [24] to estimating survival after the development of metastatic, castration-independent disease [25], there are no contemporary tools that predict sexual function, urinary incontinence, and other functional outcomes after undergoing AS, EBRT, or RP. Alemozaffar et al [26] previously attempted to predict sexual function 2 yr after treatment; however, their model focused on a small population treated with open prostatectomy at a tertiary care center and did not explore the other functional domains. Furthermore, our team previously reported 3-yr functional outcomes after AS, EBRT, and RP [3], and other studies have emphasized the harms of prostate cancer treatment [27]. These studies, however, have been limited by being able to generalize only to the studied population at whole, rather than individualizing on patient-specific factors. The National Health Services (NHS) Prostate Predict Tool uses CEASAR data to predict sexual function, but it neither took into account patient-specific information when building the model, nor addressed the other EPIC-26 patient-reported functional outcomes [28].

This study is important for several reasons. First, given the favorable long-term survival seen for localized prostate cancer, understanding patient-specific harms from treatment is critical, as is being able to assimilate this into a tool that is not overbearing to complete. Ideally, the more information we put into a model, the more reflective it is of an expected outcome, but after a certain point, the majority of the variation can be explained by the input provided. For each of the five domains on the EPIC-26, the adjusted R-squared values were comparable between the full and final models. For example, inclusion of BMI in the model for the

urinary incontinence domain changes the adjusted R-squared value to 0.233 from 0.231, which is a nonsignificant difference. Second, this web-based tool is user friendly and takes <10 min to complete. The majority of time is spent completing the EPIC-26, whereas the baseline patient information section takes <1 min to complete. By being easy to use, this tool increases the likelihood of its use. Third, this tool displays the results in graphical and numerical display, and also shows expected results through 5 yr, after which long-term side effects are unlikely to improve. This format allows patients to easily visualize what the expected side effects from treatment may be, to help guide them in selecting a treatment that is consistent with their preferences and expectations.

Nevertheless, despite the strengths of this study, several limitations need to be acknowledged. First, the creation of a patient-specific predictive tool depends on its development cohort, and despite prospective data collection, predictive tool modeling itself represents a retrospective statistical methodological approach [29]. In this study, however, we use a multicenter, contemporary, and diverse population-based patient cohort that is reflective of and salient to today's patients. Second, despite several studies demonstrating that nomograms and patient-specific predictive tools are more accurate than expert clinicians [30], many of these tools have limited overall utility and are not frequently used. Nevertheless, this web-based tool is already routinely used in our practice and made available for patients to access on their own. From a health economic and medical perspective, a small increase in predictive accuracy translates into a clinically important number of patients being provided with more accurate predictions. Third, prospective validation and adjustment are imperative, especially as certain predictors were removed to reduce the burden of completing the tool. Fourth, there are additional predictors that could be accounted for, including hormonal therapy, nerve sparing, and type of radiation treatment. Future studies with more patients in the following categories are needed to create an accurate prediction tool for these measures. Fifth, although we feel that this tool is not overburdening to the patient, differences in health literacy may affect interpretation. As such, we recommend filling this out with a provider. Finally, its clinical applicability in different clinical settings outside where the data were obtained must be viewed with caution, and some may find the actual domain score interpretation opaque. Nevertheless, our previous work has provided interpretation into how domain scores translate into functional outcomes, adding improved clarity into these clinically relevant items [31].

We strongly believe that this personalized, web-based tool provides valuable information to aid in helping clarify expected functional outcomes after AS, EBRT, and RP for localized prostate cancer. In light of this tool, we advocate for its use when counseling men on the associated harms of treatment for localized prostate cancer. This personalized prediction allows for better interpretation of patient-specific factors that affect patient-reported outcomes downstream, allowing providers to individualize these results. With predicted survival for localized disease being excellent, it is necessary to understand the risks of expected functional outcome impairment with treatment.

5. Conclusions

Functional outcomes after treatment for localized prostate cancer, including urinary incontinence and irritation, and sexual, hormonal, and bowel function, can be predicted at the time of diagnosis based on age, race, PSA, biopsy grade, baseline function, and a general question regarding overall health, pending further validation in a prospective setting. We have successfully created an online tool that both patients and providers alike can use to understand expected outcomes after treatment, further moving the pendulum toward improving shared decision making.

***Author contributions*:** Aaron A. Laviana had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Laviana, Zhao, Huang, Koyama, Ralph Conwill, Hoffman, Goodman, Hamilton, Wu, Paddock, Stroup, Cooperberg, Hashibe, O'Neil, Kaplan, Greenfield, Penson, Barocas.
Acquisition of data: Laviana, Zhao, Huang, Koyama, Conwill, Hoffman, Goodman, Hamilton, Wu, Paddock, Stroup, Cooperberg, Hashibe, O'Neil, Kaplan, Greenfield, Penson, Barocas.
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Drafting of the manuscript: Laviana, Zhao, Huang, Koyama, Conwill, Hoffman, Goodman, Hamilton, Wu, Paddock, Stroup, Cooperberg, Hashibe, O'Neil, Kaplan, Greenfield, Penson, Barocas.
Critical revision of the manuscript for important intellectual content: Laviana, Zhao, Huang, Koyama, Conwill, Hoffman, Goodman, Hamilton, Wu, Paddock, Stroup, Cooperberg, Hashibe, O'Neil, Kaplan, Greenfield, Penson, Barocas.
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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.02.007.

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